enous and endogenous substances on the binding profile of drugs to AGP, the in vitro to in vivo correlations of free level determination, and the reliability of the free level determination. We have also studied what precautions should be taken in order to upgrade the reliability of the determination of the free concentration, and we have examined the role the physical-chemical properties of isolated samples of AGP play in results of in vitro binding studies. The binding of several therapeutic classes of drugs to AGP is reviewed. The value of the use of AGP as a diagnostic and prognostic acid in disease states is reviewed as well.

II. Isolation, Structure, and Physical-Chemical Properties of Alpha-1-acid Glycoprotein

AGP, also called orosomucoid, has been a subject of study for more than 90 yr (257, 258, 396, 469). In table 1, a survey of these studies on AGP is given.

The isolation, the structure, and the physical-chemical properties of AGP have been reviewed earlier (257, 258, 469, 578). From these review studies it has become clear that there are several forms of AGP which differ in their structure and physical chemical properties. These forms have been described in terms of their physical-chemical properties (table 2).

Native AGP, asialo or desialylated AGP, modified AGP, and abnormal AGP are heterogeneous forms of AGP which differ in their molecular weight and/or electrophoretic pattern (tables 3 and 4). The molecular weight of native AGP, modified AGP, and abnormal AGP is about the same, whereas that of desialylated or asialo-AGP is lower (table 3). The amount of polymer that forms in native AGP during isolation determines the molecular weight of the polymers of AGP. The several heterogeneous forms of AGP have electrophoretic patterns which differ in the number of bands, in the moving velocities of these bands, and in the intensities of these bands, because of small charge differences in the peptide chain and carbohydrate moiety of AGP (table 4). AGP samples with different electrophoretic patterns are generally reported as different microheterogeneous types of AGP or simply as the occurring polymorphism of AGP (469). In the literature the names of heterogeneous forms or variants of AGP are sometimes, incorrectly, used to denote microheterogeneous types of AGP (469).

In this section the physical-chemical properties of several variants of AGP, such as molecular weight, stability, and microheterogeneity, will be reviewed.

A. *Methods for Isolating Alpha-1-acid Glycoprotein*

Many studies dealing with methods for isolating AGP have been reported (54, 94, 98, 119, 173, 213, 219, 257, 258, 297, 298, 306, 319, 320, 334, 388, 469, 484, 560, 570, 579, 593, 594). All the procedures described are time consuming due to the use of a series of sequential chromatographic and/or precipitation steps. Recently two- and three-step purification methods, starting from Cohn Fraction VI, have been reported (217, 303, 505). Succari et al. (515) reported recently on a two-step purification method starting from plasma itself. Because in this procedure exposure to strongly acidic conditions was prevented, the investigators could obtain an AGP sample which had not undergone desialylation. Hellerstein et al. (225) recently described a time-saving isolation method

TABLE 1
Survey of the history of the studies on AGP

No.	Subject	Period	Ref.
I	Isolation and characterization	From 1882 until about the 1960s;	54, 98, 173, 257, 258, 297, 298, 334, 466, 468, 469, 476, 484, 486, 512, 560, 570, 579, 593, 594
		again from the end of the 1970s, due to the observation that the physical-chemical properties of AGP are dependent on the isolation procedures used	12, 23, 97, 102, 123, 217, 225, 300, 515; section II
II	AGP as acute phase protein	The 1960s and the 1970s	129, 137, 152, 196, 199, 293, 446; section III
III	AGP as drug carrier for steroids	The 1960s	181, 182, 565
IV	AGP as acute phase protein and as diagnostic and prognostic aid during therapy of several disease states	Since the 1980s	164, 165, 178, 184, 221, 472, 553; section III A
V	AGP as drug carrier, especially for basic drugs;	Since the 1980s	396, 412, 460
	as drug carrier for some acidic drugs		249, 544, 545; section IV

TABLE 2
Surveys of the several names and variants of AGP

Survey of the several names used for AGP

No.	Name	Origin name	Period used	Ref.
I	*Tierisches Gummi*	Carbohydrate substance, isolated from blood, with properties identical to those of Tier-gummi (297), a mucoid isolated from snails	Sporadically, 1892	173, 297, 431
II	Seromucoid	Mucoid isolated from serum with properties comparable to those of ovomucoid, a mucoid isolated from eggs [ovum (Latin) = egg]	Always until about 1960, later sporadically	27, 173, 221, 257, 258, 273, 431, 548, 578, 593, 594
III	Alpha-1-acid glycoprotein	Acid plasma protein classified as an alpha-1-globulin and with a low isoelectric point (3.4) and a molecular weight of about 40,000	Since 1942 the name most often used	334, 475, and most refs. of table 6
IV	Mucoprotein	Glycoprotein with 30% to 50% carbohydrates	Very sporadically, about 1950	500, 560, 578, 579
V	Orosomucoid	Mucoid isolated from serum, with a high solubility in boiling water (98); [oros (Greek) = aqueous part of blood]	Since 1950 often used	53, 56, 57, 70, 93, 98, 199, 208, 211–213, 274, 302, 488, 560, 570
VI	Alpha-1-glycoprotein of Schultze	Alpha-1-glycoprotein with a molecular weight of about 54,000, first described by Schultze et al. (484)	Very sporadically, 1955, 1963	152, 484

No.	Species	Defined as	Ref.
I	Native AGP	Isolated from plasma or serum, and probably with the same properties as in vivo	53, 102, 107, 179, 213, 267, 268, 311, 371, 372, 388, 499, 500, 582
II	Delipidated or defatted AGP	AGP with a lower content of fatty acids than native AGP, resulting from ethanolic or charcoal treatment	97, 107, 181, 211, 212, 213, 282, 285
III	Asialo- or desialylated AGP	Native AGP from which essentially all sialic acid groups of the carbohydrate groups are removed enzymatically; but sometimes called modified AGP	20, 21, 50, 53, 73, 74, 102, 124, 177, 211, 268, 356, 421, 494, 499, 582
IV	Modified AGP	Native AGP from which amino acid groups of the peptide chains are modified; also sometimes used for asialo-AGP	53, 181, 259, 294, 335, 419, 489, 490, 499, 555
V	Abnormal AGP	Native AGP, isolated from serum or plasma of patients, with physical-chemical properties different from native AGP isolated from serum of healthy people	73, 74, 104, 140, 162, 215, 250, 323, 392, 448, 489, 490, 595–598
VI	Polymers of AGP	Polymers of native AGP formed during its isolation and/or purification; degree of polymerization depends on the procedures used	35, 212, 508, 569, 571
VII	Microheterogeneous types of AGP = polymorphism of AGP	Variants or heterogeneous forms of AGP (this table, nos. I–VI) with differences in their electrophoretic patterns (different number of bands, different velocity of these bands, and/or different intensity of these bands)	14, 15, 489, 490, 494, 529, see also refs. to table 4

TABLE 3

Survey of reported molecular weights for AGP

No.	Method used	Remarks on the AGP preparation used	Values	Ref.
I	Diffusion-viscosity	Native AGP, isolated according to Weimer et al. (560)	44,100	500
II	Light scattering	Two different forms of AGP, referred to as "alpha₁-niedermolekulares Säureprotein" and "alpha₁-Glykoprotein (3.5)" or "alpha₁-acid glycoprotein of Schultze," respectively, isolated by using precipitation	40,000	152, 483, 484
			54,000	152, 483, 484
	Adsorption methods			
III	Sedimentation-diffusion	Native AGP, isolated from Cohn fraction VI by chromatography on carboxymethyl cellulose	41,600	53
	Sedimentation-viscosity	Same method	43,000	53
	Sedimentation-diffusion	Desialylated AGP, isolated as described above	38,600	53
	Sedimentation-viscosity	Same method	41,600	53
IV	Sedimentation-diffusion	Native AGP, isolated according to Weimer et al. (560)	37,700	287
	Sedimentation-viscosity	Native AGP, isolated according to Weimer et al. (560)	36,700	267
	Light scattering	Native AGP, isolated according to Weimer et al. (560)	48,000	287
V	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis	Native AGP, isolated by electrofocusing	40,000	311
VI	Osmotic pressure, sedimentation equilibrium	Native AGP, isolated according to Buergi and Schmid (94)	41,100	268
			39,000	268
	Osmotic pressure, sedimentation equilibrium	Desialylated AGP, isolated as above	34,600	268
			34,100	268
VII	Sedimentation-diffusion	Native AGP, isolated from plasma using several ion exchange chromatography methods	44,080	388
VIII	Polyacrylamide slab gel electrophoresis	Two forms of AGP, one isolated from urine, the other from lymphocytes, granulocytes, and monocytes membranes	41,000	180
			52,000	180
IX	Exclusion chromatography on Sephadex G-200	Two forms of AGP with common immunological determinants and almost identical amino acid composition but different amounts of carbohydrate, isolated from liver metastases of several tumors	45,000	104
			37,000	104
X	Not mentioned	Isolated by Behringwerke	44,100	100
XI	Polyacrylamide gel electrophoresis	Native AGP, isolated according to Ganguly et al. (182); total carbohydrate content about 47%	46,000	371, 372
XII	Polyacrylamide slab gel electrophoresis	Native AGP, isolated according to Laurell et al. (300) followed by a purification using hydroxyapatite high-pressure liquid chromatography	48,000	179

which is suitable for large numbers of small-volume samples of plasma. They pointed out that it was important to check for the possible occurrence of desialylation during the acid precipitations. Halsall et al. (213) described an isolation method for native AGP from nephrotic urine under practically physiological experimental conditions. Arnaud et al. (23) described a preparative isoelectric focusing procedure starting from albumin depleted serum, which resulted in the separation of at least seven microheterogeneous types of AGP (section D).

On studying the literature dealing with AGP, one notices that the stability, denaturation, and polymerization of AGP are hardly discussed at all in clinical, pha